Herbs and Dietary Supplements in the Prevention and Treatment of Cardiovascular Disease

Adriane Fugh-Berman, MD

Herbs and dietary supplements can have significant physiological effects. Garlic (Allium sativum) has shown beneficial lipid effects in a majority of trials; dried garlic preparations are superior to oil preparations. There is preliminary evidence that indicates that hawthorn (Crataegus species) may provide benefit in congestive heart failure. Coenzyme Q also may be of benefit in congestive heart failure. Although observational studies indicate a protective effect of dietary or supplemental vitamin E, controlled trials have not shown a beneficial effect on angina and have been mixed on whether supplementation decreases major cardiac events. Although several observational studies have noted that fish intake protects against cardiovascular disease, prospective studies are less impressive. Fish oil supplementation may have a mild beneficial effect on hypertension, but there is no effect on total cholesterol levels. Trials are inconsistent on whether fish oil reduces restenosis rates following coronary angioplasty. Carnitine appears to have beneficial effects on congestive heart failure and angina; there is also preliminary evidence that arginine may benefit patients with congestive heart failure or angina. Herbs and supplements have been associated with adverse effects and interactions; for example, garlic inhibits platelet aggregation and can cause significant anticoagulation, and the Chinese herb danshen (Salvia miltiorrhiza) appears to potentiate warfarin. Several herbs and supplements hold promise as adjuncts in the prevention and treatment of cardiovascular disease. There is a need for definitive research on the potential risks and benefits of these compounds, including appropriate dosages and formulations, and delineation of adverse events and interactions. (Prev Cardiol. 2000;3:24–32)

From the George Washington University School of Medicine, Department of Health Care Sciences, Washington, DC
Address for correspondence/reprint requests: Adriane Fugh-Berman, MD, George Washington University School of Medicine, Department of Health Care Sciences, 2150 Pennsylvania Avenue, #2B417, Washington DC 20037
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The use of herbs, vitamins, amino acids, and other dietary supplements is becoming increasingly popular. A telephone survey found that between 1990–1997, herbal remedy use increased 380% and high dose vitamin use increased 130%.[1] Among respondents, 11.7% reported using an alternative therapy for hypertension within the past year (a slightly higher number than the 10.9% that actually reported a diagnosis of hypertension). It seems safe to assume that individuals with other cardiovascular risk factors are also consuming quantities of supplements. This paper will review the evidence for herbs and dietary supplements commonly used for cardiovascular disease.

HERBS

Garlic (*Allium Sativum*)

Specific preparations of garlic (whether culinary or medicinal) retain different constituents. In raw garlic, alliin (S-allyl cysteine sulfoxide), an odorless compound, is sequestered from the enzyme aliinase. When cell membranes are breached by crushing or chopping, alliinase quickly converts alliin to allicin (diallyl thiosulfinate), an odoriferous compound with the smell that characterizes garlic. Allicin is thermally unstable and also breaks down quickly in water or oil into vinyldithiins and ajoene, so garlic oil products contain only these degradation products. Allicin (and aliin) is thought to be the most beneficial compound in terms of cardiovascular risk factors. Both are stable in dried garlic preparations, which should, therefore, be standardized to one of the two. Standardized garlic preparations are available (usually standardized to 1.3% allicin). However, the most inexpensive option is commercial garlic powder meant for cooking, which was found to be superior in allicin content to nine commercially marketed garlic tablets.[2]

Hypercholesterolemia. Two metaanalyses of controlled trials of garlic for hypercholesterolemia have been done. One metaanalysis, published in 1994, included 16 randomized controlled trials with a total of 952 subjects.[3] Twelve trials were double blind and 13 trials were placebo con-

trolled (two were treatment controlled and one compared a group that supplemented their diet with raw garlic to a group instructed to avoid dietary garlic). Eleven trials in this metaanalysis used dried garlic powder. Garlic preparations reduced total cholesterol 12% (0.77 mmol/L or 29.7 mg/dL); the effect increased progressively over three months. There was no apparent difference between a daily dose of 600 mg and a daily dose of 900 mg dried garlic powder (equivalent to 1.8–2.7g or approximately 1–3 cloves fresh garlic). Of the eight trials that measured serum triglycerides, garlic reduced triglycerides 13% (0.31 mmol/L or 12 mg/dL). High density lipoprotein (HDL) cholesterol levels were not significantly affected. A small metaanalysis of five controlled trials found that the equivalent of one-half to one clove of garlic daily lowered serum cholesterol about 9%.[4]

Clinical trials performed since the preceding metaanalyses have been mixed, with negative trials predominating. A randomized double blind crossover trial of 25 patients with moderate hypercholesterolemia found that garlic (5 mg of volatile oil in ß-cyclodextrin matrix bid x 12 weeks) did not affect total cholesterol (TC), low density lipoprotein (LDL) cholesterol, HDL, triglycerides, or markers of cholesterol synthesis.[5] Although this negative trial received much publicity, it is by no means definitive; in fact, the unusual preparation (unique to the brand tested) makes it unwise to extrapolate results to any other preparations. Allicin, a known active compound, is not stable in oil. Additionally, the unusual matrix of this preparation may have inhibited release of relevant compounds.

Other negative studies include a randomized controlled trial of 115 hypercholesterolemic patients that found no significant difference between dried garlic tablets (300 mg tid) and placebo on serum lipids, HDL, LDL, triglycerides, or apolipoproteins A and B.[6] A randomized controlled trial of 28 hypercholesterolemic patients given dried garlic tablets (300 mg tid x 12 weeks) found no significant differences in lipids or lipoproteins either between groups or from baseline.[7] A small Australian crossover study also found no effect of garlic on lipids.[8]

Garlic did not benefit hypercholesterolemic children. A randomized, placebo controlled trial in 30 subjects aged 8–18 years found that a dried garlic powder preparation (300 mg tid x 8 weeks) did not cause any significant changes in TC, LDL, triglycerides, apolipoprotein B-100, lipoprotein(a), fibrinogen, homocysteine, or blood pressure. The only significant finding was a small effect (+10%) on apolipoprotein A-1.[9]

Recent trials that indicated a benefit for garlic include a double blind crossover study of 41 moderately hypercholesterolemic men (TC between 5.7 and 7.5 mmol/dL [220–290 mg/dL]) treated with 7.2 g aged garlic extract; TC was reduced 6.1% and LDL was reduced 4.6% during garlic administration vs. placebo administration.[10] HDL levels were not significantly affected. A study of 50 hypercholesterolemic males that randomized subjects to fish oil (4 capsules tid; each capsule contained 180 mg eicosapentaenoic acid [EPA] and 120 mg docosaheaenoic [DHA]), a standardized dried garlic preparation (300 mg tid), both, or placebo, found a significant reduction in cholesterol and LDL only in the two groups that received garlic.[11]

A placebo controlled study of 35 hypercholesterolemic renal transplant patients found a mild benefit of dried garlic tablets in a dose of 680 mg bid. Over six weeks TC decreased from 290 mg/dL to 276 mg/dL and LDL levels decreased from 193 mg/dL to 181 mg/dL; benefits were maintained at 12 weeks.[12]

The mixed results of the effect of garlic on cholesterol may be partially due to variations in preparations. Although most positive trials have utilized dried garlic powder preparations, there are also several negative trials utilizing the same preparations. It is possible that garlic benefits only some subsets of the population.

Hypertension. Garlic may reduce blood pressure, but the effect is mild and there is a relative dearth of data in hypertensive patients. A metaanalysis of eight controlled trials (seven placebo controlled) with a total of 415 subjects found the general quality of trials poor. All tested the same brand of dried garlic tablets. Only three of these trials were in hypertensive patients. Results were mixed, with positive trials showing only small reductions in blood pressure.[13] A more recent trial, not included in the metaanalysis, of 41 normotensive hypercholesterolemic men treated with aged garlic extract, found a 5.5% reduction in systolic blood pressure.[10]

Arterial Elasticity. A case control study found that 101 healthy, nonsmoking adults aged 50–80 with a history of regular garlic intake (≥ 300 mg/day of standardized garlic extract for ≥ 2 years) demonstrated more aortic elasticity (measured by pulse wave velocity and pressure standardized elastic vascular resistance) than age and sex matched controls.[14] Other cardiovascular risk factors did not differ between the two groups.

Other Effects. Two studies found that alliums (which include onions as well as garlic) inhibit platelet aggregation in human blood;[15,16] another laboratory study found that allicin had the same effect.[17] Garlic also appears to have some antioxidant qualities, decreasing the susceptibility of LDL to oxidation.[18]

Adverse Reactions. Garlic can cause significant anticoagulation. Because it interferes with platelet aggregation, not the coagulation cascade, this effect will not be picked up on prothrombin time/partial thromboplastin time (PT/PTT). Bleeding may

occur, especially after surgery. The following case reports suggest this potential adverse effect. A 32 year old woman with a heavy dietary garlic intake had significant bleeding intraoperatively and postoperatively associated with a prolonged clotting time.[19] A 72 year old man who regularly consumed garlic tablets experienced significant postoperative bleeding following a transurethral resection of prostate (TURP); tests revealed platelet dysfunction.[20] A spontaneous spinal epidural hematoma resulting in paraplegia in an 87 year old patient has been attributed to chronic heavy use of garlic. Platelet count was normal but platelet dysfunction was demonstrated.[21]

Hawthorn (*Crataegus* Species)
Hawthorn fruits have been used in jams, jellies, wines, and confections, as well as medicinally. The active compounds in hawthorn are thought to be oligomeric procyanidins (also called leucoanthocyanadins or pycnogenols) and flavonoids (including hyperoside, vitexinrhamnoside, rutin, and vitexin). Flowers and leaves contain far more of the major flavones than the fruit. While there is some evidence for a beneficial effect of hawthorn on congestive heart failure (CHF), larger clinical trials are indicated.

Clinical Trials. A randomized placebo controlled trial of 78 patients with NYHA Class II heart failure found that a commercial preparation of hawthorn leaves and flowers resulted in increased working capacity and decreased symptoms at one and two months.[22] In the group receiving hawthorn (200 mg tid), working capacity by bicycle ergometry increased significantly from 79 W at baseline to 107 W two months later (benefits were apparent at one month). The placebo group increased from 71 W at baseline to 76 W at two months. Systolic blood pressure (at maximal exercise) decreased from 171 mm Hg to 164 mm Hg in the Crataegus group; there was no significant difference in diastolic pressure.

A number of studies in the German literature have found improvement in cardiac function parameters (cardiac output, exercise tolerance, blood pressure, heart rate) with Crataegus preparations.[23] One of these trials compared hawthorn (LI132 Faros® 300 mg tid) to captopril (12.5 mg tid) in 132 patients with Class II CHF. Improvement was measured by bicycle ergometry. At eight weeks the hawthorn group increased from 83 W to 97 W, while the group receiving captopril improved from 83 W to 99 W. Hawthorn was associated with fewer side effects than captopril.[24]

Animal and In Vitro Studies. In a rat model, hawthorn reduced reperfusion induced ventricular fibrillation. In rats subjected to left coronary artery ischemia for seven minutes, followed by reperfusion for 15 minutes, ventricular fibrillation occurred in <20% of animals receiving hawthorn extract (0.5 mg/kg or 5 mg/kg), compared to 88% of the animals in the control group.[25] In isolated rat myocardial cells, hawthorn extract increased both amplitude and duration of cell contractions in a dose dependent manner (30–120 μg/mL); at higher doses (90–180 μg/mL), the extract lengthened the refractory period from 144 minutes to 420 minutes.[25] Hawthorn was tested in isolated normal and atherosclerotic segments taken from human coronary arteries of heart transplant patients and resulted in 14% relaxation in normal arterial segments and 8% relaxation in atherosclerotic segments.[25]

Adverse Effects. Hawthorn appears to be quite safe; only minor side effects (nausea, headache, palpitations) have been noted in clinical trials. There is a theoretical concern that hawthorn may potentiate the effect of cardiac glycosides, but no cases of interactions have been reported.

Amla (*Emblica Officinalis*)
Amla (also called Indian gooseberry), is an Ayurvedic herb used to treat hypercholesterolemia. In an uncontrolled study, 50 g of raw Amla was found to lower cholesterol in 35 men[26] (only some of whom were hypercholesterolemic). After a month, there was significant reduction in TC and LDL levels.

Danshen (*Salvia Miltiorrhiza*)
Danshen is a Chinese herb, the root of which is used to treat cardiovascular disease; it inhibits platelet aggregation *in vitro* and *in vivo* and demonstrates hypotensive, positive inotropic, and negative chronotropic effects, as well as vasodilatory effects on coronary arteries.[27]

Danshen appears to potentiate warfarin. Two case reports of clotting abnormalities, including prolonged PT and activated partial thromboplastin time (APTT) in patients mixing danshen and warfarin have been reported: one in a 48 year old woman maintained on a varying dose of warfarin for 15 months (other medications included furosemide and digoxin) hospitalized for a chest infection,[27] and another in a 66 year old man on warfarin[28] admitted for melena (subsequently diagnosed with gastric adenocarcinoma). The latter patient also had been using a Chinese medicated oil containing 15% methyl salicylate (Kwan Loong Medicated Oil) topically. In rats, danshen appears to decrease the elimination of warfarin.[29] It would be prudent to avoid the combined use of danshen with any anticoagulant.

Aconite (*Aconitum* Species)
Aconite tubers are used medicinally in traditional Chinese and Ayurvedic medicine for various illnesses, including heart failure. No clinical trials were identified and the herb is included here because of its cardiovascular toxicity. Aconite is the most toxic herb in current medicinal use.

Aconite (also called "chuanwu" or "caowu") contains aconitine and other C_{19} diterpenoid alkaloids. Although proper processing reduces the alkaloid content to 10% of its original level,[30] any amount can cause cardiac arrhythmias; severe poisoning has been observed following ingestion of a preparation containing as little as 6 g of cured rootstocks.[31] The first symptoms of aconite poisoning appear within 90 minutes of ingesting the herb.[31] The majority of patients present with neurological symptoms, most commonly oral numbness or burning, progressing to peripheral paraesthesias and generalized muscle weakness. Nausea and vomiting are also common.

Cardiovascular effects include bradycardia, hypotension, and a range of arrhythmias similar to that caused by cardiac glycoside toxicity. These may include ventricular or supraventricular tachycardia, sinus bradycardia with first degree heart block, bundle branch block with junctional escape rhythm, or torsade de pointes.[31] Bidirectional tachycardia has also been reported.[32] Other symptoms may include chest pain, abdominal pain, diarrhea, hyperventilation, respiratory distress, dizziness, sweating, confusion, headache, and excessive lacrimation.[31]

In a case series of 17 Chinese patients (12 men and five women) with aconite toxicity, 15 patients were hypotensive on admission (six with unrecordable blood pressure), two patients had ventricular fibrillation, 13 had ventricular tachycardia (nine sustained, nine polymorphic) and two patients had frequent polymorphic ventricular ectopics.[31] Nine patients had an elevated serum creatine kinase (without electrocardiographic evidence of acute myocardial infarction) and four had hypokalemia. Eleven patients required high dose inotropic support, seven required cardiopulmonary resuscitation, and eight were mechanically ventilated. Repeated direct current cardioversions were unsuccessful in 10 patients. From one to nine antiarrythmic drugs had been administered to 11 patients, without success (lignocaine was given to all, amiodarone to five, and bretylium to three). Ventricular tachycardia was eventually suppressed in nine patients (five of whom received amiodarone, two flecanainide, one procainamide, and one mexiletine). In this series, 15 patients were stabilized within 24 hours and recovered without sequelae; two patients with refractory ventricular fibrillation died within six hours of admission.

Patients with suspected aconite poisoning should be hospitalized in units with cardiac monitoring. Ventricular arrhythmias are most frequent in the first 24 hours after injection. There is no specific antidote for aconite poisoning. Atropine may be given if symptoms of cholinergic excess are apparent.[31] Antiarrhythmic drugs may be helpful in converting aconite induced arrhythmias, but it is not clear that one agent is better than another. Direct current cardioversion has been unsuccesful in reported cases.

DIETARY SUPPLEMENTS

Coenzyme Q_{10}

Coenzyme Q_{10} (CoQ_{10}) also called ubiquinone, is a naturally occurring fat soluble quinone found in high concentrations in mitochondria. It is an electron carrier for the respiratory transport chain and appears to be important in membrane stabilization. In its reduced form, it is an antioxidant. A number of trials indicate that it may have cardioprotective effects.

Recent Myocardial Infarction. A placebo controlled study in 144 patients after acute myocardial infarction tested the effect of 120 mg/day of CoQ_{10} for four weeks.[33] The incidence of angina was less in the treated group compared to the placebo group (9.5% vs. 28.1%). Total arrhythmias (9.5% vs. 25.3%) and total cardiac events, including nonfatal infarction and cardiac deaths, were also significantly reduced in the treated group (15% vs. 30.9%).

Congestive Heart Failure. Six hundred forty one patients with CHF (NYHA Class III or IV) were randomized to CoQ_{10} (2 mg/kg) or placebo for one year. Compared to placebo, fewer patients in the treated group required hospitalization for worsening CHF (73 vs. 118). Episodes of pulmonary edema (20 vs. 51) and cardiac asthma (97 vs. 198) were also less.[34] In 79 patients with chronic stable CHF, a double blind placebo controlled crossover study compared CoQ_{10} (100 mg) or placebo, each for three months. Left ventricular ejection fraction did not increase significantly, but maximal exercise capacity increased significantly (from 94 W during placebo to 100 W during CoQ_{10}) and total quality of life scores increased significantly during the CoQ_{10} phase.[35] However, a more recent trial found no effect of CoQ_{10} on left ventricular function in patients with CHF. In a double blind crossover trial in which 30 patients with ischemic or idiopathic dilated cardiomyopathy and chronic left ventricular dysfunction (ejection fraction 26%) were treated with placebo or CoQ_{10}, each for three months, CoQ_{10} did not significantly improve resting left ventricular systolic function or quality of life indices.[36]

Tissue Reperfusion Injury. A preoperative course of CoQ_{10} may have a beneficial effect in preventing tissue reperfusion injury. Thirty patients undergoing elective vascular surgery requiring aortic cross clamping were randomized to CoQ_{10} 150 mg/day or placebo for seven days preoperatively. Concentrations of malondialdehyde, conjugated dienes, creatine kinase, and lactate dehydrogenase were significantly lower in the treated group.[37] Short term supplementation, however, does not appear to help postoperative outcomes. A randomized, double blind trial compared placebo to 600 mg CoQ_{10}, in divided doses, 12 hours before surgery,

in 20 patients with adequate left ventricular function undergoing elective coronary revascularization. There was no difference between the two groups in postoperative levels of myoglobin, creatine kinase MB fraction, or cardiac troponin T.[38]

Adverse Events. Adverse effects of CoQ_{10} have been limited to occasional reports of gastrointestinal upset.

Vitamin E

Vitamin E is a fat soluble vitamin found in vegetable oils, nuts, seeds, whole grains, and egg yolks. Vitamin E includes eight compounds in two classes, the tocopherols and tocotrienols, which vary in their effects. Vitamin E appears to inhibit LDL oxidation, proliferation of smooth muscle cells, and platelet aggregation and adhesion.

Coronary Heart Disease. While several observational studies have linked vitamin E intake with reduced risk of coronary heart disease, there are few prospective controlled trials in this area. The best known epidemiological studies will be summarized briefly.

In the Health Professionals Follow Up Study, which followed 39,910 male health professionals, 40–75 years old, dietary or supplemental vitamin E was associated with a protective effect. Men who consumed >60 IU/day of vitamin E in their diets had a risk of coronary heart disease 36% lower than men who consumed <7.5 IU/day. Men who took vitamin E supplements containing at least 100 IU for >2 years had a 37% decreased risk of cardiovascular disease.[39]

In the Nurses Health Study, which included 87,245 women followed prospectively, vitamin E supplements taken for >2 years were associated with a 41% reduction in relative risk of major coronary disease.[40] A study of 34,486 postmenopausal women found that vitamin E consumption was inversely related to the risk of death from coronary heart disease,[41] and in a study of 11,178 people, aged 67–105 years, the use of vitamin E supplements was associated with a 34% lower mortality rate, and a 47% reduction in cardiovascular mortality.[42]

Secondary Prevention of Myocardial Infarction. Controlled trials have yielded mixed results on the benefits of vitamin E supplementation. In the Cambridge Heart Antioxidant Study(CHAOS), 2002 patients with coronary artery disease were given vitamin E (400 or 800 IU α-tocopherol) or placebo. Vitamin E reduced nonfatal myocardial infarction (MI) by 77% compared to placebo but did not have a beneficial effect on cardiovascular deaths or all cause mortality.[43] The Alpha Tocopherol Beta Carotene (ATBC) Cancer Prevention Study was a randomized controlled trial that tested vitamin E, ß-carotene, or both against placebo in 29,133 male Finnish smokers. Within a subset of 1862 men with a previous MI, there were no significant differences between groups in the number of major coronary events.[44]

Angina. Vitamin E supplementation does not appear to benefit angina. In the ATBC Cancer Prevention Study neither vitamin E (50 mg) nor ß-carotene (20 mg) had a beneficial effect on new incidence of angina in 22,269 men considered free of coronary heart disease at baseline.[45] In a placebo controlled trial in 60 patients with coronary spastic angina, vitamin E (α-tocopherol acetate 300 mg/day) improved endothelium dependent vasodilation significantly but the number of anginal attacks did not differ significantly between the groups.[46] Another double blind, placebo controlled crossover study, of vitamin E (1000 IU/day) in 20 asymptomatic subjects aged 45–70 years with evidence of age related endothelial dysfunction, found no significant effect of 10 weeks of treatment with vitamin E on flow mediated endothelium dependent dilatation, nor were there significant changes in glyceryl trinitrate endothelium independent dilatation.[47]

Nitrate Tolerance. A double blind, placebo controlled trial of the effect of vitamin E on the development of nitrate tolerance tested 48 subjects (24 normal volunteers and 24 patients with ischemic heart disease).[48] Forearm plethysmography was used to assess vasodilator response to nitroglycerin; at the same time, blood was sampled to assess platelet cGMP levels. Compared to placebo, the administration of vitamin E (200 mg tid) significantly attenuated the development of nitrate tolerance.

Adverse Effects. Vitamin E appears to be relatively safe. Although there is concern about vitamin E possibly increasing the risk of bleeding, a recent report found that vitamin E (all-rac-alpha tocopherol in doses of 60, 200, or 800 IU for four months) did not increase bleeding time in 88 healthy subjects >65 years old.[49] Although the tocopherols include α-, β-, gamma-, and delta-tocopherol, most vitamin E supplements sold contain only d- or d,l-α tocopherol. It may actually be a disadvantage to take large doses of α-tocopherol. Gamma-tocopherol (the principal form of dietary vitamin E in the U.S. diet) appears to be very important in protecting against peroxynitrite induced lipid oxidation, and large doses of α-tocopherol displace gamma-tocopherol in plasma and tissues.[50]

Fish Oil

Dark meat fish (including salmon, mackerel, bluefish, swordfish, and sardines) are highest in omega-3 fatty acids. Tuna and cod liver oil are also good sources; other fish and shellfish contain lesser but significant amounts. Fish oil contains the

omega-3 fatty acids EPA and DHA, which appear to have antiarrhythmic, antithrombotic, and mild antihypertensive effects.[51]

Of 10 prospective cohort studies, six have reported an inverse relationship between consumption of fish and cardiovascular mortality.[52] In the Physicians Health Study, a prospective cohort study of 20,551 U.S. male physicians, dietary fish intake was associated with a reduced risk of sudden death.[51] However, very few prospective trials have examined the effects of fish oil supplements on cardiovascular risk factors or the course of coronary heart disease.

Hypercholesterolemia. A review of 36 crossover studies and 20 parallel design studies of the effect of fish oils on lipids concluded that fish oils significantly lower triacylglycerol concentrations, but that while very low density lipoprotein (VLDL) concentrations decrease, LDL cholesterol increases slightly.[53] HDL cholesterol is unaffected and there is no net effect on total cholesterol.

Hypertension. A metaanalysis of 31 placebo controlled trials in 1356 subjects examined the effect of fish oil on blood pressure.[54] The mean reduction in systolic blood pressure was 3.0 mm Hg and the mean reduction in diastolic blood pressure 1.5 mm Hg. Doses ranged from <3 g/day to 15 g/day, and there appeared to be a dose response relationship in hypertensive patients. In contrast, there was no effect on blood pressure in normotensive subjects.

Restenosis After Coronary Angioplasty. Although a small metaanalysis of four trials concluded that fish oil reduced restenosis rates after coronary angioplasty,[55] more recent studies have not supported this and the evidence is considered mixed. In one randomized controlled trial, 59 patients with angiographically documented coronary heart disease and normal lipid levels were randomized to placebo (olive oil) or fish oil (6 g daily) for an average of 28 months.[56] Fish oil lowered triglycerides 30%, but had no effect on plasma lipids. Minimal lumen diameter decreased slightly and stenosis increased in both groups. There was no significant difference between groups.

In a 2 x 2 factorial trial that tested fish oil with or without low molecular weight heparin, 814 patients were randomized to fish oils (5.4 g omega-3 fatty acids) or placebo a median of 6 days before angioplasty and continued for 18 weeks.[57] Of the patients 653 were later randomized to low molecular weight heparin or control. Quantitative coronary angiography was performed at about 18 weeks. There were no significant differences between groups in terms of restenosis rates, minimal lumen diameter, or ischemic events.

In a placebo controlled, double blind study, 500 patients were randomized to omega-3 fatty acids 5.1 g/day or placebo (corn oil) starting at least two weeks prior to elective coronary angioplasty.[58] Treatment was continued for six months, after which quantitative coronary angiography was done. Restenosis was not reduced in the fish oil group compared to the placebo group. One study found a mild benefit. Of the patients with angiographically documented coronary heart disease 220 received fish oil or placebo (6 g daily for three months and then 3 g daily for 21 months).[59] Angiograms were evaluated in 164 patients at two years. Of the 80 patients who remained in the placebo group, 36 coronary segments showed mild disease progression, five showed moderate progression, and seven showed mild regression. In the 82 patients who remained in the fish oil group, 35 showed mild progression, four showed moderate progression, 14 showed mild regression, and two showed moderate regression. There was no difference in minimal lumen diameter, cardiovascular events, or other variables.

Secondary Prevention of Cardiac Events. A randomized controlled trial compared placebo to fish oil (containing EPA 1.08 g/day) or mustard oil (a source of α-linolenic acid, 2.9 g/day) in 360 patients with suspected MI.[60] After one year, total cardiac events were less in both treatment groups: 24.5% in the fish oil group and 28% in the mustard oil group compared to 34.7% in the placebo group.

Adverse Events. Gastrointestinal side effects have been associated with fish oil. There is also one case of lipoid pneumonia in a 63 year old woman who took cod liver oil capsules (the patient also smoked and had symptoms suggestive of esophageal reflux).[61]

Arginine

Arginine, a nonessential amino acid, is found in meats, sea food, eggs, dairy products, nuts, beans, whole grains, and gelatin. An intermediate in the urea cycle, it is also a precursor for nitric oxide and creatine phosphate. Arginine may have beneficial effects on arterial function but studies are limited.

A randomized, double blind, crossover study in 15 subjects with moderate to severe heart failure found that oral L-arginine hydrochloride (5.6–12.6 g daily) increased distance covered in the six minute walking test from 390 feet to 422 feet, and lowered scores on the Living with Heart Failure questionnaire from 55 to 42.[62] In this survey, arginine also increased forearm blood flow during forearm exercise, improved arterial compliance, and reduced circulating levels of endothelin. In a randomized, double blind crossover study in 27 hypercholesterolemic subjects, arginine (7 g tid for four weeks) significantly improved endothelium dependent dilation.[63] Arterial diameter in the brachial artery was assessed by ß-mode ultrasound

images; reactive hyperemia was used to assess endothelium dependent vasodilation, and sublingual glyceryl trinitrate was employed to assess endothelium independent vasodilation.

In another trial, 26 patients with recurrent chest pain, but without significant coronary artery disease on coronary angiography and intravascular ultrasound, were randomized to placebo or 3 g arginine tid for six months.[64] Compared to placebo, coronary blood flow in response to acetylcholine increased significantly in the treatment group; this was associated with decreased endothelin concentrations as well as symptomatic improvement.

Adverse Events. No significant adverse effects of arginine have been reported.

Carnitine

Carnitine is a nonessential nutrient formed in the liver and kidney from the amino acids lysine and methionine. A carrier molecule vital to lipid metabolism, carnitine is necessary for the transport of long chain fatty acids into mitochondria for ß-oxidation and may be a promising adjunctive treatment for patients with coronary artery disease.

Heart Failure. A placebo controlled trial in 50 patients with left ventricular dysfunction (NYHA Class II, ejection fraction <45%) found that the group receiving L-propionylcarnitine (500 mg tid for six months) showed improvements in left ventricular shortening fraction, left ventricular ejection fraction, stroke volume, cardiac index, and systemic vascular resistance. No changes in hemodynamic function were seen in the placebo group. Both groups improved in exercise time, but the increase in the carnitine group (1.4 minutes) was significantly more than that of the placebo group (0.36 minutes).[65]

Recent Myocardial Infarction. An open label trial of patients with recent MI compared 81 patients receiving carnitine (2 g bid for a year) and conventional treatment to 79 controls treated with conventional therapies only.[66] The carnitine treated group had lower mortality (1.2% vs. 12.5%), fewer anginal attacks and arrhythmias, and improvement in heart rate, systolic (but not diastolic) blood pressure, and lipid profiles.

Angina. A randomized, double blind, placebo controlled trial of L-propionylcarnitine (500 mg tid for 6 weeks) in 74 patients with >2 anginal attacks a week despite antianginal therapy, found that carnitine increased the time to ST segment depression and total exercise time. Heart rate, blood pressure, maximal exercise, and number of anginal attacks were not affected.[67]

A randomized crossover trial that compared diltiazem (180 mg qd for three weeks, then 360 mg for three weeks) to L-propionylcarnitine (1500 mg qd for six weeks) in 46 patients with stable, exercise induced angina, found that both treatments were beneficial in terms of decreasing ischemic effects, but that diltiazem was more effective than carnitine.[68] Both treatments improved exercise duration and time to ST depression. Diltiazem decreased rate pressure product at rest and exercise, and increased time to onset of angina by 22%; L-propionylcarnitine did not affect either parameter. During the study, diltiazem decreased anginal attacks by 57%, while L-propionylcarnitine decreased attacks by 70%. Patients on diltiazem decreased nitroglycerin consumption by 70%, while those on L-propionylcarnitine decreased nitroglycerin consumption by 57%.

A randomized, double blind crossover trial of 44 men with stable chronic angina found improvements in exercise tolerance in those treated with carnitine (1 g bid) compared to placebo. Maximal exercise increased significantly and less ischemic depression was seen during L-carnitine treatment than during placebo treatment. There were no differences in blood pressure, heart rate, or time to ST segment depression.[69]

Adverse Effects. L-carnitine is relatively safe. Side effects reported from trials of this substance include diarrhea and agitation. D-carnitine, however, has been associated with muscle pain and decreased physical performance.

CONCLUSION

Several herbs and dietary supplements, including garlic, CoQ_{10}, carnitine, and arginine, hold promise in the treatment of cardiovascular risk factors and should be tested in large randomized primary and secondary prevention trials. As herbs and dietary supplements are nonpatentable entities, pharmaceutical companies cannot be expected to fund these trials; public sector funding is needed in this area.

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